Supplementary Table 4. Summary of functionally enriched terms based on Mitonetwork and IPA

This table comprises of three tabs:

A) IPA Toxicity	List of perturbed pathways associated with troglitazone toxicity
B) 14 days	Summary of functional enrichment after 14 days of troglitazone administration based on Mitonetwork
C) 28 days	Summary of functional enrichment after 28 days of troglitazone administration based on Mitonetwork

A) IPA toxicity

Ingenuity Toxicity Lists	**-Log *P***
Mitochondrial Dysfunction	3.6E01
Fatty Acid Metabolism	2.62E01
LPS/IL-1 Mediated Inhibition of RXR Function	4.86E00
Oxidative Stress	1.74E00
Cytochrome P450 Panel - Substrate is a Xenobiotic (Rat)	1.53E00
PXR/RXR Activation	1.53E00

Proteins
HSD17B10, SDHB (includes EG:6390), NDUFA9 (includes EG:4704), NDUFA10 (includes EG:4705), PRDX5, NDUFB5, COX5B, NDUFB10, PDHA1 (includes EG:5160), NDUFB9, MAOB, NDUFS1, SOD2, NDUFS6 (includes EG:4726), CYB5R3, UQCRFS1, NDUFS2, OGDH, COX4I1, NDUFS4, AIFM1, NDUFA8, COX1, SDHA (includes EG:6389), NDUFV1, COX6B1, NDUFB3, CPT1A, NDUFS7, COX6C, NDUFA13, PRDX3, NDUFS8, NDUFV2, NDUFA6, UQCRC2, COX5A, COX2, UQCRC1, NDUFA7
HSD17B10, ALDH4A1, ACAA2, GCDH, HADHB, ALDH2, CYP1A2, CYP2E1, PECI, ALDH3A2, ACAD8, ACADM, HSD17B4, ALDH5A1, HADHA, ALDH1B1, CPT1A, ACOX2, ACOX1, CYP2A12, ECH1, ACAD9, DCI, ALDH9A1, ACADS, ACADL, CYP4A14, ACADVL, ACAT1, CPT2, EHHADH, IVD, ACSL1, HADH
ALDH4A1, ALDH1B1, CPT1A, ACOX2, ACOX1, CYP2A12, HMGCS2, ALDH9A1, CYP4A14, MAOB, ALDH3A2, CPT2, FABP1, ACSL1, ALDH5A1, GSTK1
PRDX3, SOD2, PRDX5, CYP2E1, GPX1
CYP1A2, CYP2E1, CYP2A12
CYP1A2, CPT1A, CES3, ALDH3A2, HMGCS2

B) 14 days no expansion

Largest connected component

Cat
Ctsb
Ctsd
Dbi
Hsd17b4
Ndufs4
Abcd3
Scp2

GO-term	**Data Proportion**	**Global Proportion**	***P* -value**	**FDR RATE**	**EXPECTED FALSE POSITIVES**	**Gene Names**
cellular lipid metabolic process	4 of 8 genes, 50.0%	618 of 33893 genes, 1.8%	0.00068	0.00%	0	Dbi, Cat, Scp2, Hsd17b4
oxidation-reduction process	4 of 8 genes, 50.0%	761 of 33893 genes, 2.2%	0.00156	0.00%	0	Ndufs4, Dbi, Cat, Hsd17b4
lipid metabolic process	4 of 8 genes, 50.0%	862 of 33893 genes, 2.5%	0.00254	0.00%	0	Dbi, Cat, Scp2, Hsd17b4
fatty acid beta-oxidation	2 of 8 genes, 25.0%	39 of 33893 genes, 0.1%	0.00341	0.50%	0.02	Dbi, Hsd17b4
fatty acid catabolic process	2 of 8 genes, 25.0%	50 of 33893 genes, 0.1%	0.00564	0.80%	0.04	Dbi, Hsd17b4
monocarboxylic acid catabolic process	2 of 8 genes, 25.0%	53 of 33893 genes, 0.2%	0.00634	0.67%	0.04	Dbi, Hsd17b4
cellular catabolic process	4 of 8 genes, 50.0%	1126 of 33893 genes, 3.3%	0.00724	0.57%	0.04	Dbi, Cat, Ctsd, Hsd17b4

C) 28 days no expansion

Largest connected component

Gldc
Cyb5
Actg1
Prdx3
Asah1
Cat
Ctsb
Ctsd
AC160930.1
Glud1
Pdia3
Hspa5
Hsd17b10
Hrsp12
Hsd17b4
Phyh
Grpel1
P4hb
Pcx
Psap
Abcd3
Scp2
Sod1
Sod2
Gm11808
Uba52
2810422J05Rik
Dhrs4
Aass
Clpp
Pmpcb
Ehhadh

GO-term	**Data Proportion**	**Global Proportion**	***P*-value**	**FDR RATE**	**EXPECTED FALSE POSITIVES**	**Gene Names**
oxidation-reduction process	13 of 32 genes, 40.6%	761 of 33893 genes, 2.2%	2.30E-11	0.00%	0	Ehhadh, Hsd17b10, Sod2, Dhrs4, Cat, Glud1, Phyh, Prdx3, Aass, Cyb5, Hsd17b4, Sod1, Gldc
primary metabolic process	26 of 32 genes, 81.2%	7095 of 33893 genes, 20.9%	1.47E-10	0.00%	0	Hspa5, Dhrs4, Scp2, P4hb, Glud1, Ctsd, Prdx3, Hsd17b4, Sod1, Asah1, Pcx, Ehhadh, Hsd17b10, Sod2, Pdia3, Cat, Pmpcb, Clpp, Ctsb, Phyh, Grpel1, Aass, Uba52, Psap, Cyb5, Gldc
carboxylic acid metabolic process	11 of 32 genes, 34.4%	648 of 33893 genes, 1.9%	3.03E-09	0.00%	0	Pcx, Ehhadh, Sod2, P4hb, Glud1, Phyh, Aass, Cyb5, Hsd17b4, Gldc, Sod1
oxoacid metabolic process	11 of 32 genes, 34.4%	648 of 33893 genes, 1.9%	3.03E-09	0.00%	0	Pcx, Ehhadh, Sod2, P4hb, Glud1, Phyh, Aass, Cyb5, Hsd17b4, Gldc, Sod1
cellular catabolic process	13 of 32 genes, 40.6%	1126 of 33893 genes, 3.3%	3.19E-09	0.00%	0	Ehhadh, Hspa5, Cat, Glud1, Ctsd, Clpp, Phyh, Prdx3, Aass, Uba52, Hsd17b4, Sod1, Gldc
organic acid metabolic process	11 of 32 genes, 34.4%	662 of 33893 genes, 2.0%	3.81E-09	0.00%	0	Pcx, Ehhadh, Sod2, P4hb, Glud1, Phyh, Aass, Cyb5, Hsd17b4, Gldc, Sod1
cellular ketone metabolic process	11 of 32 genes, 34.4%	670 of 33893 genes, 2.0%	4.33E-09	0.00%	0	Pcx, Ehhadh, Sod2, P4hb, Glud1, Phyh, Aass, Cyb5, Hsd17b4, Gldc, Sod1
metabolic process	26 of 32 genes, 81.2%	8164 of 33893 genes, 24.1%	4.52E-09	0.00%	0	Hspa5, Dhrs4, Scp2, P4hb, Glud1, Ctsd, Prdx3, Hsd17b4, Sod1, Asah1, Pcx, Ehhadh, Hsd17b10, Sod2, Pdia3, Cat, Pmpcb, Clpp, Ctsb, Phyh, Grpel1, Aass, Uba52, Psap, Cyb5, Gldc
catabolic process	13 of 32 genes, 40.6%	1355 of 33893 genes, 4.0%	3.17E-08	0.00%	0	Ehhadh, Hspa5, Cat, Glud1, Ctsd, Clpp, Phyh, Prdx3, Aass, Uba52, Hsd17b4, Sod1, Gldc
lipid metabolic process	11 of 32 genes, 34.4%	862 of 33893 genes, 2.5%	6.31E-08	0.00%	0	Pcx, Asah1, Ehhadh, Dhrs4, Cat, Scp2, Phyh, Cyb5, Hsd17b4, Psap, Sod1
small molecule metabolic process	14 of 32 genes, 43.8%	1810 of 33893 genes, 5.3%	8.17E-08	0.00%	0	Pcx, Ehhadh, Sod2, Pdia3, Dhrs4, Cat, P4hb, Glud1, Phyh, Aass, Cyb5, Hsd17b4, Sod1, Gldc
cellular metabolic process	23 of 32 genes, 71.9%	6998 of 33893 genes, 20.6%	1.94E-07	0.00%	0	Hspa5, Dhrs4, Scp2, P4hb, Glud1, Ctsd, Prdx3, Hsd17b4, Sod1, Pcx, Ehhadh, Hsd17b10, Sod2, Pdia3, Cat, Clpp, Phyh, Grpel1, Aass, Uba52, Cyb5, Psap, Gldc
organic acid catabolic process	6 of 32 genes, 18.8%	122 of 33893 genes, 0.4%	4.75E-07	0.00%	0	Ehhadh, Phyh, Aass, Glud1, Hsd17b4, Gldc
carboxylic acid catabolic process	6 of 32 genes, 18.8%	122 of 33893 genes, 0.4%	4.75E-07	0.00%	0	Ehhadh, Phyh, Aass, Glud1, Hsd17b4, Gldc
hydrogen peroxide metabolic process	4 of 32 genes, 12.5%	29 of 33893 genes, 0.1%	4.50E-06	0.00%	0	Sod2, Prdx3, Cat, Sod1
cellular response to reactive oxygen species	4 of 32 genes, 12.5%	40 of 33893 genes, 0.1%	1.72E-05	0.00%	0	Sod2, Prdx3, Cat, Sod1

cellular lipid metabolic process	8 of 32 genes, 25.0%	618 of 33893 genes, 1.8%	2.46E-05	0.00%	0	Ehhadh, Dhrs4, Cat, Scp2, Phyh, Cyb5, Hsd17b4, Psap
response to hydrogen peroxide	4 of 32 genes, 12.5%	47 of 33893 genes, 0.1%	3.34E-05	0.00%	0	Sod2, Prdx3, Cat, Sod1
cellular amino acid metabolic process	6 of 32 genes, 18.8%	273 of 33893 genes, 0.8%	5.79E-05	0.00%	0	Sod2, Aass, P4hb, Glud1, Sod1, Gldc
reactive oxygen species metabolic process	4 of 32 genes, 12.5%	57 of 33893 genes, 0.2%	7.36E-05	0.00%	0	Sod2, Prdx3, Cat, Sod1
cellular process	26 of 32 genes, 81.2%	12361 of 33893 genes, 36.5%	8.08E-05	0.00%	0	Abcd3, Hspa5, Dhrs4, Scp2, P4hb, Glud1, Ctsd, Prdx3, Hsd17b4, Sod1, Pcx, Ehhadh, Hsd17b10, Sod2, Pdia3, Cat, Clpp, Actg1, Ctsb, Phyh, Grpel1, Aass, Uba52, Cyb5, Psap, Gldc
negative regulation of cell death	7 of 32 genes, 21.9%	487 of 33893 genes, 1.4%	8.81E-05	0.00%	0	Hspa5, Ctsb, Sod2, Prdx3, Cat, Uba52, Sod1
cellular response to oxidative stress	4 of 32 genes, 12.5%	62 of 33893 genes, 0.2%	0.0001	0.00%	0	Sod2, Prdx3, Cat, Sod1
regulation of mitochondrial membrane potential	3 of 32 genes, 9.4%	18 of 33893 genes, 0.1%	0.00018	0.00%	0	Sod2, Prdx3, Sod1
response to reactive oxygen species	4 of 32 genes, 12.5%	72 of 33893 genes, 0.2%	0.00018	0.00%	0	Sod2, Prdx3, Cat, Sod1
monocarboxylic acid metabolic process	6 of 32 genes, 18.8%	351 of 33893 genes, 1.0%	0.00025	0.00%	0	Pcx, Ehhadh, Phyh, P4hb, Hsd17b4, Cyb5
cellular amine metabolic process	6 of 32 genes, 18.8%	353 of 33893 genes, 1.0%	0.00026	0.00%	0	Sod2, Aass, P4hb, Glud1, Sod1, Gldc
amine metabolic process	6 of 32 genes, 18.8%	429 of 33893 genes, 1.3%	0.0008	0.00%	0	Sod2, Aass, P4hb, Glud1, Sod1, Gldc
regulation of cell death	8 of 32 genes, 25.0%	1019 of 33893 genes, 3.0%	0.00106	0.00%	0	Hspa5, Ctsb, Sod2, Pdia3, Prdx3, Cat, Uba52, Sod1
negative regulation of apoptosis	6 of 32 genes, 18.8%	462 of 33893 genes, 1.4%	0.00122	0.00%	0	Hspa5, Sod2, Prdx3, Cat, Uba52, Sod1
negative regulation of programmed cell death	6 of 32 genes, 18.8%	468 of 33893 genes, 1.4%	0.00132	0.00%	0	Hspa5, Sod2, Prdx3, Cat, Uba52, Sod1
response to nutrient levels	4 of 32 genes, 12.5%	154 of 33893 genes, 0.5%	0.00393	0.00%	0	Hspa5, Sod2, Ctsd, Sod1
small molecule catabolic process	6 of 32 genes, 18.8%	574 of 33893 genes, 1.7%	0.00422	0.00%	0	Ehhadh, Phyh, Aass, Glud1, Hsd17b4, Gldc
fatty acid catabolic process	3 of 32 genes, 9.4%	50 of 33893 genes, 0.1%	0.00428	0.00%	0	Ehhadh, Phyh, Hsd17b4
response to oxidative stress	4 of 32 genes, 12.5%	162 of 33893 genes, 0.5%	0.0048	0.00%	0	Sod2, Prdx3, Cat, Sod1

monocarboxylic acid catabolic process	3 of 32 genes, 9.4%	53 of 33893 genes, 0.2%	0.00511	0.00%	0	Ehhadh, Phyh, Hsd17b4
hydrogen peroxide biosynthetic process	2 of 32 genes, 6.2%	7 of 33893 genes, 0.0%	0.00533	0.05%	0.02	Sod2, Sod1
cell death	8 of 32 genes, 25.0%	1305 of 33893 genes, 3.9%	0.00642	0.05%	0.02	Hspa5, Ctsb, Sod2, Pdia3, Prdx3, Cat, Uba52, Sod1
death	8 of 32 genes, 25.0%	1313 of 33893 genes, 3.9%	0.00671	0.05%	0.02	Hspa5, Ctsb, Sod2, Pdia3, Prdx3, Cat, Uba52, Sod1
response to extracellular stimulus	4 of 32 genes, 12.5%	177 of 33893 genes, 0.5%	0.0068	0.05%	0.02	Hspa5, Sod2, Ctsd, Sod1
cell redox homeostasis	3 of 32 genes, 9.4%	63 of 33893 genes, 0.2%	0.00861	0.10%	0.04	Pdia3, Prdx3, P4hb
regulation of apoptosis	7 of 32 genes, 21.9%	985 of 33893 genes, 2.9%	0.00901	0.10%	0.04	Hspa5, Sod2, Pdia3, Prdx3, Cat, Uba52, Sod1
regulation of programmed cell death	7 of 32 genes, 21.9%	996 of 33893 genes, 2.9%	0.00967	0.09%	0.04	Hspa5, Sod2, Pdia3, Prdx3, Cat, Uba52, Sod1
cellular amino acid catabolic process	3 of 32 genes, 9.4%	66 of 33893 genes, 0.2%	0.00991	0.09%	0.04	Aass, Glud1, Gldc